

| eCB<br>signaling in ASD  | Subjects<br>/System<br>model  | Major<br>Effects   |    | Study  |
|--|---|--|----|--|
| Circulating AEA, PEA and<br>OEA  | Children with<br>ASD  | Reduced serum<br>levels unchanged<br>ASD symptoms                      | ↓  | Aran et al.,<br>2019   |
| MAGL inhibition and<br>increase of eCB signaling<br>in BLA-NAc circuit | SHANK3 mouse<br>model   | Decreased<br>deficits in<br>social behavior<br>and social<br>avoidance | ↓  | Folkes et al.,<br>2020   |
| CBD-enriched oil   | SHANK3 mouse<br>model   | Decreased ASD-<br>like behavior<br>(e.g., social<br>anxiety)           | ↓  | Poleg et al.,<br>2021  |
| CBD-enriched oil   | Children with<br>ASD  | Improvement of<br>symptoms<br>(hyperactivity,<br>social abilities)     | ↑  | Ponton et al.,<br>2020<br><br>Loss et al.,<br>2021<br><br>Bar-Lev<br>Schleider et<br>al., 2019 |
| PEA supplementation  | Children with<br>ASD  | Improvement<br>language skills   | ↑  | Antonucci et<br>al., 2015  |
| Ultramicronized PEA +<br>Luteolin coadministration                     | VPA-induced<br>ASD-like mice  | Improvement of<br>social behavior                                      | ↑  | Bertolino et<br>al., 2017  |
| Ultramicronized PEA +<br>Luteolin coadministration                     | 10 year old<br>male children  | Stereotypies<br>decrease<br>Improvement of<br>ASD symptoms             | ↓  | Bertolino et<br>al., 2017  |
| FAAH inhibition/increase<br>of AEA-signaling                           | <i>fmr1</i> /FMRP KO<br>mouse model/<br><br>ASD-like<br>BTBR mouse<br>model | Reversion of<br>social deficit<br>(both models)                        | ↺↻ | Wei et al.,<br>2016  |

|  |                        |   |                            |                         |
|--|------------------------|---|----------------------------|-------------------------|
| Prenatal VPA exposure/effects in adolescent rats | ASD-like VPA rat model | <p>Decreased DAGL-<math>\alpha</math> activity/reduced 2-AG synthesis (cerebellum)</p> <p>Hippocampal enhancement of MAGL activity</p> <p>Social exposure induces AEA, PEA and OEA increase</p> | <p>↓</p> <p>↑</p> <p>↑</p> | Kerr et al., 2013       |
| Prenatal VPA exposure                            | ASD-like VPA rat model | <p>Decrease of NAPE-PLD expression/</p> <p>Increase of AEA degradation/</p> <p>Deficits social play and communication</p>   | <p>↓</p> <p>↑</p> <p>↑</p> | Servadio et al., 2016   |
| Pharmacological FAAH inhibition                  | ASD-like VPA rat model | Reduced VPA-induced deficits in social behavior   | ↓                          | Kerr et al., 2016       |
| PBMCs  | ASD patients           | Up-regulation of CB <sub>2</sub> receptors  | ↑                          | Siniscalco et al., 2013 |

**TABLE 1**

Summary table of the key studies showing involvement of eCB signaling in ASD.